CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-081

CORRESPONDENCE

RECORD OF TELEPHONE Date: CONVERSATION/MEETING June 4, 1999 Re: 4/9/99 submission NDA #: 21-081 I called Dr. Patton and conveyed the following request from Telecon/Meeting Dr. Wei. These requests were included in Dr. Wei's 6/2/99 initiated by: memorandum. **FDA** 1. Please submit Section 6 summary (Human By: Telephone Pharmacokinetics and Bioavailability) on disc in MS Word format. Product Name: LANTUSTM 2. Submit on disc individual study summaries (text and tables) in Section 6 in MS Word format. Firm Name: Hoechst Marion Roussel, Inc. I asked Dr. Patton to use either Office 97 or 6.0 Word format. Name and Title of Person Dr. Patton agreed to get back to me with a timeline when we with whom conversation could expect the requested Word documents. was held: Lavonne Patton, Ph.D. cc:OrigNDA Regulatory Affairs HFD-510/DivFile Quintiles HFD-870/Wei US agent for Hoechst p.s. The package insert was submitted on a disc as Word document. Phone: (816) 767-6674

Name: Julie Rhee

MEMORANDUM OF FILING MEETING MINUTES

Meeting Date:

June 2, 1999

Application: NDA 21-081 Lantus (insulin glargine injection [rDNA origin])

Sponsor:

Hoechst Marion Roussel, Inc.

Attendees:

Solomon Sobel, M.D., Director, DMEDP

Robert Misbin, M.D., Medical Officer, DMEDP

Ronald Steigerwalt, Ph.D., Pharmacology Team Leader, DMEDP

Herman Rhee, Ph.D., Pharmacology Reviewer, DMEDP Todd Sahlroot, Ph.D., Statistical Team leader, DOB II

Jonathan Ma, Ph.D., Statistician, DOB II

Hae-Young Ahn, Ph.D., Biopharm Team Leader, DPE II

Jim Wei, Ph.D., Biopharm reviewer, DPE II

Julie Rhee, Project Manager, DMEDP

Discussion Points:

Clinical:

- 1. The NDA is fileable as a standard application.
- 2. Advisory Committee meeting is not necessary.
- Statistical review is needed for type 1 indication only. 3.
- 4. Dr. Misbin is amenable to have the Division of Scientific Investigation choose the clinical audit sites from Study 3001 or Study 3004.

Pharmacology:

The application is fileable.

Statistical:

- 1. The application is fileable.
- 2. There are five Phase 3 studies (three studies for type 1 and two studies for type 2 indication). Medical Officer agreed that review of only type 1 indication would be acceptable.
- 3. Ask the sponsor to submit study reports from studies 3001, 3004, and 3005 in Word format.
- 4. Ask the sponsor to submit a hard copy of carcinogenicity study reports.

Biopharm:

The application is fileable.

Chemistry:

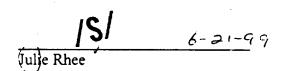
Dr. Berlin was not able to attend the filing meeting but informed me that the NDA is fileable by e-mail (attached).

Microbiology:

Dr. Stinavage informed me that the NDA is fileable by e-mail (attached).

Conclusion:

- 1. The NDA is filed as a standard application.
- 2. Advisory Committee meeting is not necessary for this NDA. machang
- Statistical review of type 1 indication only would be acceptable. 3.
- 4. Clinical audit sites are to be chosen by DSI from either Study 3001 or 3004.
- 5. The NDA is NME with UF₁₀ due date of February 23, 2000. The following is a list of target dates:
 - ◆ January 7, 2000: Final review with team leader's concurrence
 - ♦ January 18, 2000: Action package to Dr. Sobel
 - January 31, 2000: Action package to Dr. Jenkins
- 6. The company's Information Technology contact person is



- Attachments: 1. Summary of studies prepared by Dr. Jonathan Ma, HFD-715
 - 2. E-mail from Dr. Berlin
 - 3. E-mail from Dr. Stinavage

cc:OrigNDA

HFD-510/DivFile

HFD-510/Malozowski/Misbin/Moore/Berlin/Steigerwalt/HRhee

HFD-715/Sahlroot/Ma

HFD-870/Ahn/Wei

HFD-160/Cooney/Stinavage

R/D by: JRhee 6/3/99

Concurred by: Steigerwalt 6-4-99/Sahlroot 6-4-99/Ahn 6-17-99/Ma 6-18-99/Wei 6-18-

99/Misbin 6-21-99/HRhee 6-21-99

F/T by: JRhee 6-21-99

Meeting Minutes

NDA 21-081

Drug name: Lantus (insuline glargine injection)

Applicant: Hoechst Marion Roussel, Inc. Indication: Treatment of —— diabetes

User fee date: 23 February 2000 Statistics reviewer: Z. Jonathan Ma, Ph.D.

Date6/2/99

	3001	3004			
Overall Design	Parallel-	trolled, Randomized, Open-label, Group, Phase III			
Study Treatment	HOE 901 once daily, individuall	y titrated, plus regular insulin injections.			
Control Treatment	NPH once or twice daily, individua	ally titrated, plus regular insulin injections.			
Duration of Treatment	1 2	18 weeks			
Patient Population	Type 1 diabetic subjects: >1 yr ins	Type 1 diabetic subjects: >1 yr insulin trt; C-peptide<0.5 nmol/L; GHb≤12%			
Primary Efficacy Endpoint	GHb: change from baseline to 28 weeks or study endpoint Hypoglycemia; fasting glucose (FPG;SMBG); 24-hr blood glucose profile; variability of fasting glucose; insulin dose. (3001 had nocturnal bood glucose)				
Secondary Efficacy Endpoints					
Sample Size	585 (292 HOE 901, 293 NPH)	534 (264 HOE 901, 270 NPH)			
No. of Centers	63 in 12 European countries	49 in US			
Primary Efficacy Analysis					
ANCOVA model	Change in GHb at endpoint = treatme	nt + (pooled) center + baseline GHb			
ITT population	557 (283 HOE 901, 274 NPH)	518 (256 HOE 901, 262 NPH)			
GHb (%): adj mean chg from baseline at endpoint	0.21 (0.053) vs 0.10 (0.053)	-0.16 (0.05) vs -0.21 (0.049)			
Difference in adj mean chg	0.11	0.05 (0.069)			
95% Confidence Interval	(-0.03, 0.24)	(-0.08, 0.19)			

	Summary of Study 3005
Overall Design	Multi-center, Active-Controlled, Randomized, Open-label, Parallel-Group, Phase III
Study Treatment	HOE 901 once daily, individually titrated, plus regular insulin injections.
Control Treatment	NPH once or twice daily, individually titrated, plus regular insulin injections.
Duration of Treatment	16 weeks
Patient Population	Type 1 diabetic subjects: >1 yr daily insulin and NPH and Lispro for 3 months
	C-peptide<0.5 nmol/L; GHb≤12%
Primary Efficacy Endpoint	GHb: change from baseline
Secondary Efficacy Endpoints	Hypoglycemia; fasting glucose (FPG;SMBG); 24-hr blood glucose profile; variability of fasting glucose; insulin dose.
Sample Size	619 (310 HOE 901, 319 NPH)
No. of Centers	60 in US and Canada

Summary of Study 3006				
Overall Design	Multi-center, Active-Controlled, Randomized, Open-label, Parallel-Group, Phase III			
Study Treatment	HOE 901 once daily, individually titrated, with/without regular insulin injections			
Control Treatment	NPH once or twice daily, individually titrated, with/without regular insulin injections.			
Duration of Treatment	28 weeks			
Patient Population	Type 2 diabetic subjects: >3 months insulin; GHb 7-12%; BMI<40 kg/m2			
Primary Efficacy Endpoint	GHb: change from baseline			
Secondary Efficacy Endpoints	Hypoglycemia; fasting glucose (FPG;SMBG); variability of fasting glucose; fasting serum C-peptide; fasting serum insulin; insulin dose.			
Sample Size	518 (259 HOE 901, 259 NPH)			
No. of Centers	60 in US and Canada			

	Summary of Study 3002
Overall Design	Multi-center, Active-Controlled, Randomized, Open-label, Parallel-Group, Phase III
Study Treatment	HOE 901 once daily, individually titrated, combined with OAD.
Control Treatment	NPH once or twice daily, individually titrated, combined with OAD.
Duration of Treatment	20 weeks
Patient Population	Type 2 diabetic subjects: >1 yr OAD; inadequate for >3 months with current OAD or insulin treatment; GHb 7.5-12%; BMI<40 kg/m2
Primary Efficacy Endpoint	GHb: change from baseline
Secondary Efficacy Endpoints	Hypoglycemia; fasting glucose (FPG;SMBG); nocturnal bood gucose; 24-hi blood glucose profile; variability of fasting glucose; fasting serum C-peptide fasting serum insulin; insulin dose.
Sample Size	570 (289 HOE 901, 281 NPH)
No. of Centers	57 in 14 European countries

ELECTRONIC MAIL MESSAGE

sensitivity: COMPANY CONFIDENTIAL

Date:

15-Jun-1999 02:20pm EDT

From:

William Berlin

BERLINW

Dept:

HFD-510

PKLN 14B31

Tel No:

301-827-6370 FAX 301-443-2356

:O: Julie Rhee

(RHEEJ)

Subject: NDA 21-081

ulie,

have reviewed the contents of the above NDA and have concluded that dequate information has been provided for the CMC section to permit iling.

Printed by Julie Rhee

Electronic Mail Message

Date: 02-Jun-1999 03:18pm
From: Paul Stinavage
STINAVAGEP

Dept: HFD-160 PKLN 18B08
Tel No: 301-827-7340 FAX 301-443-9281

O: Julie Rhee (RHEEJ)

subject: FWD: Re: NDAs 21-081 filing meeting
hey're both (NDA's 21-081 filable.

aul

AC meeting was not held for Lantus



Quintiles 10245 Hickman Mills Drive P. O. Box 9708 Kansas City, MO 64134-0708

Tel (816) 303-6000 Fax (816) 966 3594

US Drug Regulatory Affairs

MERC Team (Metabolism, Endocrinology, Rheumatology, Cardiovascular)

MERC Team Members: Carol Blanton,
Marguerite Enlow, Sharon Huffman,
Philip Kastner, Michelle Kliewer,
Lavonne Patton, Cindy Vick,
Susan Zordan

To: Julie Rhee		From:	Susan Zordan	
Company:	FDA	Date:	March 15, 2000	
Fax No:	301 443-9282	Page 1 of :	12	

Comments: Copies of three submissions to

NDA 21-081

Julie,

Attached are copies of the three submissions to NDA 21-081 which we discussed earlier today:

- 1. withdrawal Mailed 3/13/2000
- 2. Precautionary statement for mixing of Lantus with Regular Insulin Mailed 3/15/2000
- 3. Outline of the educational program for health care professionals and patients Mailed 3/15/2000

Sue

APPEARS THIS WAY ON ORIGINAL

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

Form Approved OMB No. 0910-0338 Expiration Date: April 30, 2000 See OMB Statement on page 2.

FOR	FDA	USE	ONL	١.
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APPLICATION NUMBER

(Title 21, Code of I	Federal Regulations, 314 & (601)	
APPLICANT INFORMATION			·
NAME OF APPLICANT		DATE OF SUBMISSION	
Aventis Pharmaceuticals Inc.		3/13/	2000
TELEPHONE NO (Include Area Code) (816; 966-5000		FACSIMILE (FAX) Number (816) 966-6794	(Include Area Code)
APPLICANT ADDRESS (Number, Street, City, St.	ste. Country, ZIP Code or Mail Code, an	AUTHORIZED U 6. AGENT N.	AME & ADDRESS (Number, Street, City, State, ZIP)
U.S. License number II previously issued).		Code, relephone & FAX number	
10236 Marion Park Drive Kansas City, Missouri 64134-0627		P.O. Box 9708	7-6674 or FAX: (816) 767-7373
Natisas City, Wissouti 64134-0627		Kansas City, MO 64134	4-0708
		, and do so	
		1	
PRODUCT DESCRIPTION			
NEW DRUG OR ANTIBIOTIC APPLICATION NUI	MARE OR BIOLOGICS LICENSE APP	LICATION NUMBER (Kommously	vissued) NDA 21-081
ESTABLISHED NAME (e.g., Proper name, USPA)		PROPRIETARY NAME (trade n	
		LANTUSTM	
INSUINE GIBITUNE INJECTION CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT N			CODE NAME (If any)
21A-Gly-30Ba-L-Arg-30Bb-L-Arg-h		·	HOE 901
DOSAGE FORM.	STRENGTHS:		UTE OF ADMINISTRATION: boutan e ous
Injection PROPOSED; INDICATION(S) FOR USE:	100 U/mL	500	xuaneous
LAYCOSTM is an insulin analog indicated for one who require basa! (long-acting) insulin for the col		the treatment of palients with type	1 or type 2 diabetes mellitus
APPLICATION INFORMATION			
APPLICATION TYPE Check one Service New Drug APPLICA BIOL	OGICS LICENSE APPLICATION (21 C	REVIATED APPLICATION (AND DFR part 601)	IA, AADA, 21 CFR 314.94)
IF AN NOA, IDENTIFY THE APPROPRIATE TYP	E 🔀 505 (b) (1) ☐ 5	505 (b) (2)	
IF AN ANCAL OR AACAL IDENTIFY THE REFER Name of Drug	ENCE LISTED DRUG PRODUCT THA Holder of Approv		AISSION
TYPE OF SUBMISSION ORIGINAL APP	PUCATION X AMENDMEN	NT TO A PENDING APPLICATION	RESUBMISSION
FRESUBMISSION ANNUA	L REPORT ESTAB	BUSHMENT DESCRIPTION SUPPLEM	MENT SUPAC SUPPLEMENT
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REASON FOR SUBMISSION			
withd	lrawal.		
PROPOSED MARKETING STATUS (check on		Axt OVER-THE-CO	OUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED N/A			PAPER AND ELECTRONIC ELECTRONIC
ESTABLISHMENT INFORMATION	THIS APPLICATION IS		
Provide locations of all manufacturing, packaging		-d days need of (excellention the	ate may be used if necessary). Include name.
andress, contact, telephone number, registration conducted at the site. Please indicate whether the	number (CFN), DMF number, and man	ulacturing steps and/or type of te	sting (e.g. Final dosage form, Stability testing)
See original New Drug Application dated	4/09/99		
Cross References (list related License A	ipplications, INDs, NDAs, PMAs	, 510(k)s, IDEs, BMFs and I	DMFs referenced in the current
application)			
See original New Drug Application dated	4/09/99		

This application contains the following items: (Ch	eck all that apply)	•						
1. Index								
2. Labeling (check one)	2. Labeling (check one) Draft Labeling Final Printed Labeling							
3 Summary (21 CFR 314.50 (c))	3 Summary (21 CFR 314.50 (c))							
4. Chemistry section								
A. Chemistry, manufacturing, and control	s information (e.g. 21 CFR 314.50 (d) (1), 21	CFR 601.2)						
	FR 601.2 (a)) (Submit only upon FDA's reque							
C Methods validation package (e.g. 21 C								
	section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 6	501.2)						
6. Human pharmacokinetics and bioavailabi	ity section (e.g. 21 CFR 314.50 (d) (3), 21 CF	FR 601.2)						
7 Clinical Microbiology (e.g. 21 CFR 314.50								
8. Clinical data section (e.g. 21 CFR 314.50	(d) (5), 21 CFR 601.2)							
9 Safety update report (e.g. 21 CFR 314.5)	·····	· · · · · · · · · · · · · · · · · · ·						
10. Statistical section. (e.g. 21 CFR 314.50 (c								
11 Case report tabulations (e.g. 21 CFR 314								
12. Case reports forms (e.g. 21 CFR 314.50								
13. Patent information on any patent which cl								
14. A patent certification with respect to any p		b) (2) or (i) (2) (A))						
15 Establishment description (21 CFR Part 6		, (L) C G, (L) , //						
16. Debarment certification (FD&C Act 306 (k								
18. User Fee Cover Sheet (Form FDA 3397)	17 Field copy certification (21 CFR 314.50 (k) (3))							
19 OTHER (Specify)								
CERTIFICATION								
1 agree to update this application with new safety information about orse reactions in the draft labelling. I agree to submit safety updates the submit safety updates are submit safety updates. It is applicable laws and regulations that apply to sport 1. Good manufacturing practice regulations in 21 CFR Part 2 Biological establishment standards in 21 CFR Part 3 Labelling regulations 21 CFR 201, 606, 610, 660 at 4. In the case of a prescription drug or biological process of the submitted of the	pdate reports as provided for by regulation or as required applications, including, but not limited to the folk 210 and 211, 605, and/or 820. 600, nd/or 809 fuct, prescription drug advertising regulations in 21 CT CFR 314-70, 314-71, 314-72, 314-97, 314-99, and 600-80 and 600-81. It does not be controlled Substances All and, to the best of my knowledge are certified to be	uested by FDA. If this applicationing. IFR 202. 601.12. ct, I agree not to market the p	nion is approved, 1 agrcc 10 3					
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE Lavonne Patton.	Ph D	DATE					
Aroni Patter	Director, Regulatory & Technical Services		3/13/2000					
ADDRESS (Street, City, State, and ZIP Code) P.O. Box 9708, Mail Station: F3-M3026	<u></u>	Telephone Number (816) 767-6000						
Public reporting burden for this collection of Information is a data sources, gathering and maintaining the data needed, and concer aspect of this collection of information, including suggestion	ompleting and reviewing the collection of information	ng the time for reviewing instr	uctions, searching existing this burden estimate or any					
DHHS Reports Clearance Officer Pagentory Registrate Propert (0930-0729)	An agency may not conduct person is not required to responsible.		•					
Paperwork Reduction Project (0910-0338) Hubort H. Humphray Building, Room 531-H	information unless it displays							
200 Independence Avenue, \$ W. «Vashingron, DC 20201	control number							
Please DO NOT RETURN this form to this address.		Please DO NOT RETURN this form to this address.						



Quintiles, Inc.
Post Office Box 9708
Kansas City, MO 64134-0708
(816) 767-6000

March 13, 2000

John Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject:

NDA 21-081

insulin glargine injection

Withdrawal

Dear Dr Jenkins:

Quintiles, Inc., as the US agent for Aventis Pharmaceuticals Inc., has been authorized to communicate with the FDA on NDA 21-081.

As requested by the Division of Metabolic and Endocrine Drug Products, Aventis

Pharmaceuticals Inc., is withdrawing from consideration for approval

as part of HOE 901 NDA 21-081. The OptiPen device will remain in the file being reviewed

Please let me know if you have any comments or concerns regarding this request.

Sincerely,

Lavorine M. Patton, Ph.D.

Haven re totter

Director, Regulatory and Technical Services

Quintiles, Inc.

10245 Hickman Mills Drive

Kansas City, MO 64137

BEST PUSSIBLE CUT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-033& Expiration Date: April 30, 2000 See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION				
NAME OF APPLICANT		DATE OF SUBMISSION		
Avenirs Pharmaceuticals Inc.		3/15/2000		
TELEPHONE NO (Include Area Code) (816) 966-5000		FACSIMILE (FAX) Numb	per (include Area Code)	
APPLICANT ADDRESS (Number, Street, City, State, Co	nuntry ZIP Code or Mail Code and	[(816) 966-6794	NAME & ADDRESS (Number Street City State 7/P	
U.S. License number if previously issued);	,, , Osde (,	Code, telephone & FAX nun		
10236 Manon Park Drive		Quintiles, Inc. (816) 7	767-6670 or FAX: (816) 767-7373	
Kansas City, Missouri 64134-0627		P.O. Box 9708		
		Kansas City, MO 641	34-0708	
PRODUCT DESCRIPTION				
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER.		ICATION NUMBER (II previou	sty issued) NDA 21-081	
ESTABLISHED NAME (e.g., Proper name, USP/USAN n	name)	PROPRIETARY NAME (trade	name) IF ANY	
insuline quargine injection		LANTUS™		
CHEMICAUBIOCHEMICAUBLOOD PRODUCT NAME /			CODE NAME (If any)	
21 ^A Gly-30 ^B s-L-Arg-30 ^B b-L-Arg-huma	PENGTHS:		HOE 901	
	DO U/mL	1	OUTE OF ADMINISTRATION: ubcutaneous	
PROPOSED INDICATION(S) FOR USE				
LANTUS** is an insulin analog indicated for once-daily who require busal flong-acting) insulin for the control of	subcutaneous administration in th hypergrycemia.	e treatment of patients with typ	pe 1 or type 2 diabetes molfitus	
APPLICATION INFORMATION				
APPLICATION TYPE				
Theck one: NEW DRUG APPLICATION (21 CFR 314.50)	EVIATED APPLICATION (AN	IDA, AADA 21 CFR 314 94)	
E BIOLOGICS	LIGENSE APPLICATION (21 C	FR part 601)		
FANCISE CENTIFY THE APPROPRIATE TYPE	Ø 505 (b) (1) ☐ 50	S (b) (2) 507		
IF AN ANDA I OR AADA I identify the reference l Nome of Divig	LISTED DRUG PRODUCT THAT Holder of Approve		BMISSION	
TYPE OF SUBMISSION DRIGINAL APPLICATIO	ON AMENDMENT	TO A PENDING APPLICATION	RESUBVISSION	
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EFFICACI SUPPLEMENT LABELIN	IG SUPPLEMENT CHI	EMISTRY WANUFACTURING AND	CONTROLS SUPPLEMENT OTHER	
REASON FOR SUBMISSION				
Provide precautionary state	ement for mixing	of Lantus with I	Regular Insulin	
PRIPOSED MARKETING STATUS (check one)	PRESCRIPTION PRODUCT (R.	C OVER-THE-	COUNTER PRODUCT (OTC)	
NUMBER OF VOLUMES SUBMITTED N/A	THIS APPLICATION IS	PAPER [PAPER AND ELECTRONIC ELECTRONIC	
ESTABLISHMENT INFORMATION	·			
Provide ocations of at manufacturing, packaging and collaborates compact telephone number, registration number				
conducted of the site. Please indicate whether the site is				
See or ginal New Drug Application dated 4/09/99	9			
Cross References (list related License Applica application)	stions, INDs, NDAs, PMAs,	510(k)s, IDEs, BMFs and	DMFs referenced in the current	
See or ginal New Drug Application dated 4/09/9	9			

This	ar	pp ic	ation contains the following i	tems: (Che	ck all tha	t apply)			
	1	1	Index					,	
·	1	2.	Labeling (check one)		ַ	Draft Labeling		Final Printed	Labeling
<u> </u>	\perp	3	Summary (21 CFR 314.50 (c))						
		4	Chemistry section						
	\perp		A. Chemistry, manufacturing,	and controls	informatio	n (e.g. 21 CFR 314.50 ((d) (1), 21 C	FR 601.2)	
			B. Samples (21 CFR 314.50 (e) (1), 21 CF	R 601.2 (a)) (Submit only upon FC	A's request)	
			C Methods validation package	e (e.g. 21 CF	R 314.50	(e) (2) (i), 21 CFR 601.2	?)		
		5.	Nondinical pharmacology and	toxicology s	ection (e.g.	. 21 CFR 314.50 (d) (2)	. 21 CFR 60	1.2)	
	\perp	6.	Human pharmacokinetics and	bioavallabilit	y section	(e.g. 21 CFR 314.50 (d)	(3), 21 CFF	9 601.2)	
	L	7.	Clinical Microbiology (e.g. 21 (FR 314.50 (d) (4))				
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)								
		9.	Safety update report (e.g. 21 (CFR 314.50	(d) (5) (vi)	(b), 21 CFR £01.2)			
		10.	Statistical section (e.g. 21 CFI	R 314.50 (d)	(6), 21 CF	R 601.2)			
		11	Case report tabulations (e.g. 2	1 CFR 314.	so (f) (1), 2	1 CFR 601.2)			~
		12.	Case reports forms (e.g. 21 C	FR 314.50 (f	(2), 21 CI	FR 601.2)			
		13	Patent information on any pate	nt which clai	ms the dru	ig (21 U.S.C. 355 (b) or	(c))		
	T	14	A patent certification with response	ect to any pa	tent which	claims the drug (21 U.	S.C 355 (b)) (2) or (j) (2) (A))	
		15	Establishment description (21 (CFR Part 60), if applica	able)			
	Γ	15	Department certification (FD&C	Act 306 (k)(1))				
		17	Field copy certification (21 CFF	314.50 (k)	(3))		1 de		
		18	User Fee Cover Sheet (Form F	DA 3397)) # ** 		
		19	OTHER (Specify)				,		
adverse comply if this a Enforce The dat	ippli	updal action h all 1 2 E 3 Life 5 F 7 Life cation	is this application with new safety infins in the draft labeling. I agree to su applicable laws and regulations that sood manufacturing practice regulations to the case of a prescription drug or bregulations on making changes in applications on making changes in applications on making changes in applications on eponts in 21 CFR 314 legulations on reports in 21 CFR 314 degulations on applications on the federal environment in applies to a drug product that FDA diministration makes a final schedular information in this submission have be fulfully false statement is a criminal of	bmit safety up apply to appro- ons in 21 CFR 21 CFR Part 6 i. 610, 660 and ological produ- plication in 21 i.80, 314.81, 6 al impact laws has proposal ig decision.	date reporta- ved applicati 210 and 21- i00. Vor 809. et prescript CFR 314.75 00.80 and 6 for schedul and, to the b-	as provided for by regulate ions, including, but not limit 1, 608, and/or 820. ion drug advertising regulat 5, 314.71, 314.72, 314.97, 3 00.81 ing under the Controlled States of my knowledge are ce	on or as reque ted to the lose tions in 21 CF 314,99, and 6 ubstances Act	peted by FDA. If this approximate: R 202 01 12. It lagree not to market to	incation is approved. Lagrec to
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<u>></u> √			m corolan for la	nowof		Regulatory & Technica			
POB	or!	9708	, Mail Station: F3-M3026	Pad			1	Falaphona Number (816) 767-6000	
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data sc	urc	es g	ng burden for this collection of inf athoring and maintaining the data no this collection of information, includ-	eded, and co	mpleting and	d reviewing the collection o	onse, includinç if information.	g the time for reviewing i Send comments regan	nstructions, searching existing ding this burden estimate or any
		-	Cisarence Officer			An agency may	not conduct	t or sponsor, and a	
			luction Project (0910-0338) phray Building, Room 531-M			information unles	iniad io iasbi se il disbibli	ond to, a collection of a currently valid OMB	
200 Ind	ep.	ce	nce Avenue, S.W			sontrol number.			
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Quintiles, Inc. Post Office Box 9708 Kansas City, MO 64134-0708 (816) 767-6000

March 15, 2000

John Jenkins, M.D.
Acting Director
Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject:

NDA 21-081

NDA Amendment

insulin glargine injection

Precautionary Statement for Mixing of Lantus with Regular Insulin

Dear Dr. Jenkins:

Quintiles, Inc., as the US agent for Aventis Pharmaceuticals Inc., has been authorized to communicate with the FDA on NDA 21-081.

During our teleconference with the FDA on March 14, 2000, the Sponsor was provided two options for approaching the issue of "mixing" HOE 901 with other insulins.

The second option was to put appropriate precautionary statements in the labeling based on the dog study to address what a patient may expect if HOE 901 is mixed with regular insulin. If this statement is placed into the precautions section of the labeling, no additional studies would be needed.

The Sponsor has determined that Option #2 above would be preferred. To that end, attached please find the statement that the Sponsor is proposing to be added to the labeling for Lantus.

avonne Pathon

Please let me know if you have any comments or questions regarding this information.

Sincerely,

Lavonne M. Patton, Ph.D.

Director. Regulatory and Technical Services

Quintiles, Inc. (Mail Stop: F3-M3026; Phone: 816-767-6674)

smh/Attachment

Proposal for Modifications to Mixing Statements in the LANTUS™ Package Insert

The following four changes, regarding not mixing Lantus with other insulins or solutions, are being proposed to be made to the sponsor's draft package insert dated February 29, 2000:

1.	PRECAUTIONS: General, second paragraph changed to read:
	LANTUS™ must not be diluted or mixed with any other insulin or solution.
	and regular human insulin were mixed immediately before injection in dogs, a delayed onset of action and time to maximum effect for regular human insulin was observed. The total bioavailability of the mixture was also slightly decreased compared to separate injections of

2. PRECAUTIONS: Information for patients, add a new second paragraph to read:

LANTUS™ and regular human insulin.

Patients must be advised that LANTUSTM must not be diluted or mixed with any other insulin or solution.

3. DOSAGE AND ADMINISTRATION: Preparation and handling, third paragraph changed to read:

Mixing and diluting. LANTUS™ must not be diluted or mixed with any other insulin or solution (See PRECAUTIONS: General).

4. DOSAGE AND ADMINISTRATION: Preparation and handling, fourth paragraph starting with to be deleted.

BEST POSSIBLE COPY

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMS No. 0910-0	338
Expiration Date: April 30, 2000	
See OMB Statement on page 2.	

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION					
NAME OF APPLICANT		DATE OF SUBMISS	DATE OF SUBMISSION		
Aventis Pharmaceuticals Inc.		3/15/2	3/15/2000		
TELEPHONE NO. (Include Aren Code) (816) 966-5000	,	FACSIMILE (FAX) N (816) 966-6794	FACSIMILE (FAX) Number (Include Area Code) (816) 966-6794		
	lly, State, Country, ZIP Code or Mail Code,	and AUTHORIZED U.S. AGE	ENT NAME & ADDRESS (Number, Street, City, S	iale. Z	
U.S. License number if previously issued); 10236 Marion Park Drive			number) IF APPLICABLE 6) 787-6674 or FAX: (816) 767-7373		
Kansas City, Missouri 64134-0627		P.O. Box 9708			
		Kansas City, MO	Kansas City, MO 64134-0708		
			•		
PRODUCT DESCRIPTION		<u> </u>			
	N NUMBER, OR BIOLOGICS LICENSE AP	PLICATION NUMBER (It pre	viously issued) NDA 21-081		
ESTABLISHED NAME (e.g., Proper name, I		PROPRIETARY NAME (I			
Insuline glargine injection	•	LANTUS**			
CHEMICAUBIOCHEMICAUBLOOD PRODU 21 ^A -Gly-30 ^B a-L-Arg-30 ^B b-L-A	JCT NAME (Wany)		CODE NAME (If any) HOE 901		
DOSAGE FORM:	ISTRENGTHS:		POUTE OF ADMINISTRATION:		
Injection	100 U/mL		Subcutaneous		
(PROPOSED) INDICATION(S) FOR USE:	or once-daily subcutaneous administration is	the best of paleons with	ham Lacken 2 dishalar melidus		
who require basel (long-acting) insulin for t	he control of hyperglycemia	n the treatment or patients wit	n type 1 of type 2 debates mentos		
APPLICATION INFORMATION					
Check one) NEW DRUG API	BIOLOGICS LICENSE APPLICATION (21	CFR part 601)	(ANDA, AADA, 21 CFR 314 94) .		
F AN ANDA, OR AADA, IDENTIFY THE RE	EFERENCE USTED DRUG PRODUCT TH	AT IS THE BASIS FOR THE			
Name of Drug	Molder of Appr	oved Application			
TYPE OF SUBMISSION Check one)	L APPLICATION AMENDM	ENT TO A PENDING APPLICATION	ON RESUBMISSION	•	
PRESUBMISSION A	UNNUAL REPORT EST.	ABLISHMENT DESCRIPTION SU	IPPLEMENT SUPAC SUPPLE	MENT	
EFFICACY SUPPLEMENT	LABELING SUPPLEMENT	CHEMISTRY MANUFACTURING	S AND CONTROLS SUPPLEMENT	THER	
REASON FOR SUBMISSION					
Provide Outline of the	he Educational Program	for Health Car	re Professionals and Pati	ent	
PROPOSED MARKETING STATUS (chec		P-12	THE-COUNTER PRODUCT (OTC)		
IUMBER OF VOLUMES SUBMITTED	N/A THIS APPLICATION I	S D PAPER	PAPER AND ELECTRONIC ELECTR	IONIC	
STABLISHMENT INFORMATION					
Provide locations of all manufacturing, pacti address, contact, telephone number, registr conducted at the site. Please indicate whet	ration number (CFN), DMF number, and ma	anulaciumng ateps and/or typi	on sheets may be used if necessary). Include has a of testing (e.g. Final dosage form, Stability testi	me, ing) -	
See original New Drug Application d	ated 4/09/99				
Cross References (list related Licer ipplication)	ise Applications, INDs, NDAs, PMA	s, 510(k)s. IDEs, BMF6	and DMFs referenced in the current		
See original New Drug Application d	ated 4/09/99	_			

This	application contains the following items: (Ch	eck all that apply)					
	1. Index						
	2 Labeling (check one)	Draft Labeling	Final Printer	d Labeling			
	3. Summary (21 CFR 314.50 (c))						
	4. Chemistry section						
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)						
	B. Samples (21 CFR 314.50 (a) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)						
	C. Methods validation peckage (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)						
	5. Nonclinical phermacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)						
	6. Human pharmacokinetics and bioevailabil						
	7. Clinical Microbiology (e.g. 21 CFR 314.50						
	8. Clinical date section (e.g. 21 CFR 314.50		· · · · · · · · · · · · · · · · · · ·				
	9. Safety update report (e.g. 21 CFR 314.50						
-	10. Statistical section (e.g. 21 CFR 314.50 (d						
	11. Case report labulations (e.g. 21 CFR 314						
	12. Case reports forms (e.g. 21 CFR 314.50 (·					
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c)) 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))						
	15 Establishment description (21 CFR Part 6)		(4) (4) (4)				
	16. Debarment certification (FD&C Act 306 (k)						
	17 Field copy certification (21 CFR 314.50 (k) (3))						
	18. User Fee Cover Sheet (Form FDA 3397) 19 OTHER (Specify)						
l agreo i adverse	FICATION o update this application with new safety information about reactions in the draft labeling. Lagree to submit safety up with all applicable laws and regulations that apply to appring the coordinate of	pdate reports as provided for by regulation or oved applications, including, but not limited to	as requested by FDA If this 2	wamings, precautions, or optication is approved. I agrice to			
The date	2 Biological establishment standards in 21 CFR Part 3 Labeting regulations 21 CFR 201, 606, 610, 660 at 4. In the case of a prescription drug or biological prod 5. Regulations on making changes in application in 2. 6. Regulations on reports in 21 CFR 314.80, 314.81, 7. Local, state and Federal environmental impact law plication applies to a drug product that FDA has propose ment Administration makes a final acheduling decision, and information in this submission have been reviewed 5. a wilfully talse statement is a criminal offense. U.S. C.	600. Mor 809. uct, prescription drug advertising regulations 1 CFR 314.70-314.71, 314.72, 314.97, 314.9 500.80 and 800.81. d for schoduling under the Controlled Substat and, to the best of my knowledge are certifie	9, and 601.12. nees Act, I agrae not to market	: the product until the Drug			
SIGNAT	URE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE Lavonne P	atton, Ph.D.	DATE			
- Sua	on Rordon dos (arounes	Director, Regulatory & Technical Ser		3/15/2000			
P.O. 50	SS (Sirely, Criy, State, and ZIP Code) 70 (1) x 9708; Mail Station: F3-M3026 City, MO 64134-0708		Telephone Number (816) 767-6000				
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Quintiles, Inc. Post Office Box 9708 Kansas City, MO 64134-0708 (816) 767-6000

March 15, 2000

John Jenkins, M.D.
Acting Director
Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject:

NDA 21-081

NDA Amendment

insulin glargine injection

Outline of the Educational Program for Health Care Professionals and Patients

Dear Dr. Jenkins:

Quintiles, Inc., as the US agent for Aventis Pharmaceuticals Inc., has been authorized to communicate with the FDA on NDA 21-081.

At the teleconference with the FDA on March 14, 2000, the FDA asked that the Sponsor provide a summary of the educational program currently being planned to educate health care professionals and patients regarding non-mixing of Lantus with other insulins. The attached document contains the Sponsor's current plan to address the educational aspects.

Please let me know if you have any comments or questions regarding this information.

Sincerely,

Susan Jordan for Laronne Patton Lavonne M. Patton, Ph.D.

Director, Regulatory and Technical Services

Quintiles, Inc. (Mail Stop: F3-M3026; Phone: 816-767-6674)

smh/Attachment

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DrAft



ORIG AMENDMENT

Quintiles, Inc. Post Office Box 9708 Kansas City, MO 64134-0708 (816) 767-6000

February 28, 2000

John Jenkins, MD Acting Director Division of Metabolic and Endocrine Drug Products Center for Drug Evaluation and Research (HFD 510) Food and Drug Administration Document Control Room 14B-04 5600 Fischers Lane Rockville, MD 20857

Subject:

NDA 21-081

insulin glargine injection

Amendment: Response to CMC questions from Dr. Moore received 2/22/2000

Dear Dr. Jenkins:

Quintiles Inc., as the US Agent for Aventis Pharmaceuticals Inc., has been authorized to communicate with the FDA on NDA 21-081.

We are submitting the enclosed response in reply to a request received February 22, 2000 from Dr. Stephen Moore. (Please see the attached list of questions received by fax from the Agency.)

A summary of the Phase IV commitments made in this response is as follows:

• •	
<u>-</u> .	The 24 month data from the primary stability studies for drug substance will be available in May 2000. That data will be submitted to the NDA and the specification limits for HOE 901content,
	901content,
	that data.
-	

If you require any additional information, please do not hesitate to contact me.

Sincerety.

Susan M. Zordan

Assistant Director, Regulatory & Technical Services

Quintiles, Inc. (Mail Stop: F3-M3026; Phone: (816) 767-6673)

smh/Attachments

REVIEWS COMPLETED_



Quintiles Inc. Post Office Box 9708 Kansas City. MO 64134-0708 (816) 767-6000

March 2, 2000

Julie Rhee
Project Manager
Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 148-04
5600 Fishers Lane
Rockville, MD 20857

Subject:

NDA 21-081

insulin glargine injection

OptiPen™ ~

Dear Julie:

Quintiles, Inc., as the US agent for Aventis Pharmaceuticals Inc., has been authorized to communicate with the FDA on NDA 21-081.

As you requested, I have enclosed two samples — of the OptiPen — insulin injection device.

Currently. Marketing plans to bring the OptiPen — insulin injection device to the US market

Please let me know if you require any additional information.

Sincerely.

Aliena Pattor

Lavonne M. Patton, Ph.D. (816) 767-6674 Director, Regulatory and Technical Services Quintiles, Inc. 10245 Hickman Mills Drive Kansas City, MO 64137

Enclosure



10245 Hickman Mills Drive P. O. Box 9708 Kansas City, MO 64134-0708

Tel (816) 767-6000 Fax (816) 767-7373

US Drug Regulatory Affairs

MERC Team (Metabolism, Endocrino ನಿರ್ಲ. Rheumatology Carciovascular.

MERC Team Members: Carol Blanton Marguerite Enlow, Sharon - Januar Philip Kastner, Michelle Krawer Lavonne Patton, Cindy Vick Susar Zordan

To:	Julie Rhee	From:	Lavonne Patton
Company:		Date:	2-9-00
Fax No:	301-443-9282	Page I of	3

180-1E AON

Comments:

Here is some background intermation for our tele conference tomorrow. I have confirmed it on our side.

Please let me know: I you have any questions.

Thank you.

Lavonne

APPEARS THIS WAY ON ORIGINAL

I.EGAL NOTICE:

This telecopy and its contents are privileged, copyrighted and contain confidential information intended only for the person(s) named above. Any other distribution, copying, review, use or disclosure is strictly prohibited. If you have received this telecopy in error, please notify us immediately by telephone and return the original transmission to us by mail without making a copy. reviewing or otherwise using for any purpose.

Mixing HOE 901 (pH \approx 4.0) with a neutral buffered solution of regular insulin will increase the pH of the entire solution. At approximately pH 5.1 - 5.3 precipitation of HOE 901 will begin to occur. Exploratory studies show that this process of an almost complete HOE 901 precipitation starts at a ratio of 95% HOE 901 and 5% regular insulin. As a result of this precipitation, the clear solution in the vial will turn into a cloudy suspension. Depending on the mixing ratio, a partial precipitation of the added regular insulin is also found.

Mixing Ratio HOE901/Insulin	рН	Visual inspection	HPLC Analysis HOE 901 % of total amount found in:		HPLC-Analysis Human Insulin % of total amount found in:	
			Supernatant	Precipitate	Supernatant	Precipitate
96.80 / 3.20	4.5	Clear solution	n.d.	n.d.	n.d.	n.d.
95 00 / 5.00	5.1	Slightly opaque	100	0	100	0
85 00 / 15.00	5.5	solution Suspension	1	99	38	62
50 00 / 50 00	6.9	Suspension	1	99	55	45
30.00 / 70.00	7.1	Suspension	1	99	78	22
2.90 / 97.10	7.3	Slightly opaque solution	100	0	100	0

Solutions with 100 IU/ml human insulin or HOE901 have been used. Insulin means our commercial regular human insulin preparation. The HOE 901 solution contains 30 µg/ml zinc.

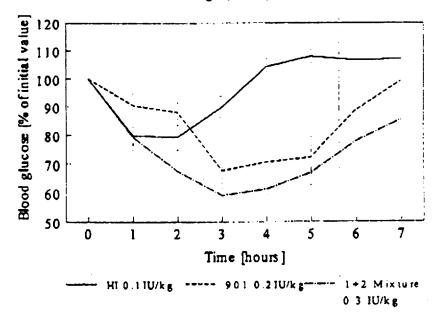
For theoretical reasons, the same should hold true for insulin lispro added in increasing concentrations to HOE 901. Similar results to those reported above for human insulin, were found with insulin lispro for visual inspection and pH measurement (no HPLC analysis was performed). This significant co-precipitation of the added soluble insulin may be explained by the fast exchange of the different insulin molecules between hexamers before or during pH-induced precipitation.

Precipitation of insulin may alter the pharmacokinetic behavior of an insulin but not its biological activity. A precipitation of HOE 901 in the vial is not expected to change its PK profile since this is what occurs at the injection site, too.

For the regular insulin a more delayed onset of action as a consequence of the co-precipitation could be expected. However, exploratory studies in dogs did not show a major change in onset of action with a mixture of HOE 901 and regular insulin in comparison to the individual injections of both insulins. Moreover, no significant decrease in total hypoglycemic effect was indicated (see Figure on next page).

HOE 901 is given at bedtime when the simultaneous injection of regular insulin or insulin lispro is very unlikely. In the very unlikely case of mixing both insulins with HOE 901 the worst case scenario would be a delayed onset to the regular insulin component. This situation is comparable to the injection of zinc-containing lente insulins with regular insulin.

Mixture (1+2) of H-Insulin and HOE 901 Dogs (n=7-8), s.c.



HOE 901 is a formulation containing 40 IU/kg HOE 901 and $\Rightarrow \mu g/ml$ zinc. HI = regular human insulin (our commercial U40 formulation).



Guinties Inc Post Office Box 9708 Kansas City MO 64134-0708 (816) 767-6000

January 18, 2000

John Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject:

NDA 21-081

NDA Amendment

insulin glargine injection

Response to question raised by Dr. Komanduri on January 11, 2000

Attention:

Dr. Pardha Komanduri

Dear Dr. Jenkins:

Quintiles, Inc., as the US agent for Hoechst Marion Roussel, has been authorized to communicate with the FDA on NDA 21-081.

The attached response is provided to address a question raised by Dr. Pardha Komanduri in our conversation of January 11, 2000. If you require any additional information, please do not hesitate to contact me at the number listed below, or Susan Zordan at (816) 767-6673.

Sincerely,

Lavonne M. Patton, Ph.D.

Flainne ketten

Director, Regulatory and Technical Services

Quantiles, Inc.

P.O. Box 9708 --F3-M3026 Kansas City, MO 64134-0708

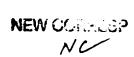
(816) 767-6674

APPEARS THIS WAY ON ORIGINAL

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Enclosure

Aventis Pharmaceuticals





January 17, 2000

Food and Drug Administration Division of Metabolism and Endocrine Drug Products (HFD-510) Document Control Room 14B-03 5600 Fishers Lane Rockville, MD 20857

Subject: NDA 21-081 **LANTUS™**

(insuline glargine injection)

GENERAL CORRESPONDEN

Company Name Change

Dear Sir/Madam:

A letter was recently forwarded to your attention regarding a name change for our corporation. "Inc." was inadvertently omitted. This letter is to inform you that the name of the corporation sponsoring the above-captioned application has been changed recently from Hoechst Marion Roussel, Inc. to Aventis Pharmaceuticals Inc. There has been no transfer of ownership of this application. Enclosed is an updated FDA Form 356h reflecting the name change.

Please be advised that there have been no other changes in relation to the studies ongoing or the responsible individuals. You will be advised if any changes occur as appropriate.

If you should have any questions or comments concerning this submission, please contact the undersigned at:

> AVENTIS PHARMACEUTICALS INC. P.O. Box 9627 Kansas City, Missouri 64134-0627

Sincerely.

J. Michael Nicholas, PhD Director, US Regulatory Affairs

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Marketed Products

816-966-5720

REVIEWS COMPLETED



ORIGINAL

NDA SUPP AMEND

Quintiles, Inc. Post Office Box 9708 Kansas City, MO 64134-0708 (816) 767-6000

January 13, 2000

John Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857



(polsoon

Subject:

NDA 21-081

insulin glargine injection

NDA Amendment

Response to questions raised by Dr. Robert Misbin on December 28, 1999

Attention:

Dr. Robert Misbin

Dear Dr. Jenkins:

Quintiles, Inc., as the US agent for Hoechst Marion Roussel, has been authorized to communicate with the FDA on NDA 21-081.

We are submitting the enclosed response in reply to a request received December 28, 1999, from Dr. Robert Misbin.

Please let me know if you require any additional information.

Sincerely,

Lavonne M. Patton, Ph.D. (816) 767-6674
Director, Regulatory and Technical Services
Quintiles, Inc.
P.O. Box 9708
Kansas City, MO 64134-0708

Enclosure

cc: Julie Rhee, Project Manager

REVIEWS COMPLETED

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DATE

DATE

Aventis Pharmaceuticals

January 10, 2000

Food and Drug Administration Division of Metabolism and Endocrine Drug Products (HFD-510) Document Control Room 14B-03 5600 Fishers Lane Rockville, MD 20857

Subject: NDA 21-081 **LANTUS™**

(insuline glargine injection)

GENERAL CORRESPONDENCE **Company Name Change**

Dear Sir/Madam:

This letter is to inform you that the name of the corporation sponsoring the abovecaptioned application has been changed recently from Hoechst Marion Roussel to Aventis Pharmaceuticals. There has been no transfer of ownership of this application. Enclosed is an updated FDA Form 356h reflecting the name change.

Please be advised that there have been no other changes in relation to the studies ongoing or the responsible individuals. You will be advised if any changes occur as appropriate.

If you should have any questions or comments concerning this submission, please contact the undersigned at:

> **AVENTIS PHARMACEUTICALS** P.O. Box 9627 Kansas City, Missouri 64134-0627

Sincerely,

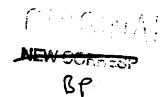
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J. Michael Nicholas, PhD Director, US Regulatory Affairs Marketed Products 816-966-5720

REVIEWS COMPLETED CSO A -M0 DATE CSO



Quintiles, Inc. Post Office Box 9708 Kansas City, MO 64134-0708 (816) 767-6000





January 6, 2000

Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD 510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject:

NDA 21-081

insulin glargine injection

Response to question received January 5, 2000 regarding incidence of hepatocellular adenomas in male NMRI mice

Attention: Herman Rhee, Ph.D.

Dear Dr. Sobel,

The following information is being provided in response to a question raised by Dr. Herman Rhee, on January 5, 2000, regarding the incidence of hepatocellular adenomas in male NMRI mice.

In the HOE 901 mouse carcinogenicity study, hepatocellular adenomas were observed in the HOE 901 vehicle control (6/50) and in the low (5/50) and intermediate (5/50) HOE 901 dose groups. In the high dose group the incidence was 1/50. The HOE 901 mouse carcinogenicity study was the first study performed in our testing facility with NMRI mice from the breeder

In the meantime a second study was conducted with the test compound _____ The incidence of hepatocellular adenoma in the two control groups of 50 male NMRI-mice (breeder: ______ each was: 3/50 and 1/50.

As mentioned in the original HOE 901 carcinogenicity study report in mice, the historical control data for male NMRI-mice received from the Registry of Industrial Toxicology Animal (RITA) database showed a range of 2.0% - 16.0% for hepatocellular adenomas (5 studies with 248 control animals). Only in one of these studies were NMRI-mice from the breeder used (study performed by another pharmaceutical company). The incidence of hepatocellular adenoma in the control group in this study was 6/50.

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In conclusion, although the database is limited, the incidence of hepatocellular adenomas in male mice in the HOE 901 carcinogenicity study is considered to be a random event, reflecting the normal biological variation of this spontaneously occurring tumor in NMRI-mice.

Please let me know if you require any additional information. Sincerely,

Lavonne M. Patton, Ph.D. (816) 767-6674

Director, Regulatory and Technical Services
Quintiles, Inc.
10245 Hickman Mills Drive
Kansas City, MO 64137

cc: Julie Rhee

REVIEWS COMPLETED	
CSO ACTION: LETTER CHAIL MEMO 1-21-00 CSO INITIALS DATE	
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Quintiles. Inc. Post Office Box 9708 Kansas City, MO 64134-0708

(816) 767-6000

January 6, 2000



Ms. Julie Rhee
Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD 510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject:

NDA 21-081

insulin glargine injection

Dear Julie,

In our telephone conversation of January 4, 2000, you requested that we provide samples of the vials that will be used to supply insulin glargine (Lantus). Enclosed you will find three samples of the 5 mL and 10 mL vial packages as you requested.

Please note that the plastic flip caps for the actual Lantus vials will be lavender instead of the colors on the enclosed vials. The sealing discs in the 10 mL vials are the new proposed sealing disc and the sealing discs in the 5 mL vials are the current sealing disc.

Also enclosed are copies of the labels, which will be used on the vials. The labels will be printed on clear stock so that the patients will be able to visually examine the insulin solution before use. The area behind the text (shown as shaded gray on these labels) will be opaque so that the printing is more legible.

Please let me know if you require any additional information.

Sincerely,

Lavonne M. Patton, Ph.D. (816) 767-6674

Director, Regulatory and Technical Services

Quintiles, Inc.

10245 Hickman Mills Drive

Kansas City, MO 64137

Horne latter

Enclosures

WITHHOLD 2 PAGE (S)

Draft Labeling



Quintiles, Inc. Post Office Box 9708 Kansas City, MO 64134-0708 (816) 767-6000

Cana in

December 22, 1999

Solomon Sobel, M.D. Director, Division of Metabolic and Endocrine Drug Products Center for Drug Evaluation and Research (HFD 510) Food and Drug Administration Document Control Room 14B-04 5600 Fishers Lane

Rockville, MD 20857

Attention:

Julie Rhee

Subject:

NDA 21-081 insulin glargine injection **Final Safety Update**

Dear Dr. Sobel:

In accordance with 21 CFR 314.50(d)(5)(vi)(b), Quintiles Inc, the US Agent for Hoechst Marion Roussel, Inc, is submitting a 2-volume Final Safety Update for NDA 21-081, insulin glargine injection. A diskette containing the updated unannotated labeling is included for your convenience.

The original NDA was received by the Agency on April 23, 1999. The 120-day Safety Update was submitted to the Agency on July 6, 1999. This Final Safety Update includes new safety information on the ongoing clinical trials. The safety update includes data through November 24, 1999.

Please call me if you have any questions regarding this submission.

Sincerely,

Hounne Youth Lavonne Patton, Ph.D. (816) 767-6674 Director, US Drug Regulatory Affairs

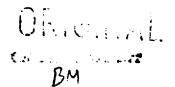
Quintiles, Inc.

10245 Hickman Mills Drive

Kansas City, MO 64137



Quintiles, Inc. Post Office Box 9708 Kansas City, MO 64134-0708 (816) 767-<u>6</u>000



December 2, 1999

Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

NAZ, ISI

Subject:

NDA 21-081

insulin glargine injection

Amendment to a pending application
Response to the request for additional clinical information

Dear Dr. Sobel:

Quintiles, Inc., as the US Agent for Hoechst Marion Roussel, has been authorized to communicate with the FDA on NDA 21-081.

The following document is being submitted in response to the request for additional clinical information received by fax on November 18, 1999, from Julie Rhee (see attached).

Please let me know if you require any additional information.

Sincerely,

Lavonne M. Pattori, Ph.D. (816) 767-6674 Director, Regulatory and Technical Services Quintiles, Inc.

P.O. Box 9708

Kansas City, MQ 64134-0708

Arionne Patton

REVIEWS GOTTON TO THE STATE OF THE STATE OF

APPEARS THIS WAY ON ORIGINAL

1, 18 /18/00



CIGINAL

BI DRIC ASALVIDAMENT

November 22, 1999



Solomon Sobel, MD
Food and Drug Administration
Division of Metabolism and Endocrine Drug Product (HFD-510)
Center for Drug Evaluation and Research
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject:

NDA 21-081

insulin glargine injection

Amendment - Response to List of Microbiology Deficiencies

Dear Dr. Sobel:

Quintiles, Inc., as the US Agent for Hoechst Marion Roussel, has been authorized to communicate with the FDA on NDA 21-081.

The following document is being submitted in response to the list of microbiology deficiencies received by fax from Julie Rhee on October 28, 1999 (see attached).

If you require any additional information, please contact me at (816) 767-6673 or Lavonne Patton at (816) 767-6674.

Sincerely,

Susan M. Zordan

Assistant Director, US Drug Regulatory Affairs

Quintiles, Inc.

smh

Attachment

REVIEWS COMPLETED

ACTION:

LETTER MAJ. MEMO

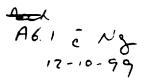
12-8-99

CSO INITIALS

DATE

Micro consult requested





DUPLICATE

MDA SUF 1/4 2

ER

Quintiles. Inc. Post Office Box 9708 Kansas Gity. MO 64134-0708 (816) 767-6000

October 21, 1999

Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD 510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857



Subject:

NDA 21-081

Insluin glargine injection

NDA Amendment Mouse Carcinogenicity Codes on Diskette

Attention:

Julie Rhee

Dear Dr. Sobel,

It was brought to my attention by the Statistical Reviewer, Dr. Moh Jee Ng, that some of the codes for the Tumor Type and Organ-Tissue Type data were missing from the preclinical carcinogenicity package provided to the FDA on April 27, 1999, in support of the HOE 901 NDA submission. All of the codes for the rat data were provided in this submission, however the codes for the mouse data were not included. To correct this oversight, I am enclosing a virus-scanned diskette and hard copy of the missing mouse tumor and organ/tissue codes.

Please let me know if you have any questions.

Sincerely,

Lavonne M. Patton, Ph.D. (816) 767-6674

1 avance toutton

Quintiles, Inc.

10245 Hickman Mills Drive Kansas City, MO 64137

APPEARS THIS WAY
ON ORIGINAL

List of Tumor Type Codes Mouse

000000	Octooms
060008	Osteoma
080006	Papilloma
090025	Adenoma bronchiolo-alveolar
090026	Carcinoma bronchiolo-alveolar
090040	Papilloma bronchial
150105	Papilloma squamous cell
150207	Adenoma
170106	Schwannoma benign
170107	Sarcoma not otherwise specified
170203	Haemangioma
180025	Haemangioma
180026	Adenoma hepatocellular
180027	Carcinoma hepatocellular
180028	Haemangiosarcoma
180045	Histiocytoma fibrous malignant
200024	Adenoma acinar cell
200026	Carcinoma islet cell
230010	Papilloma transitional cell
230011	Submucosal mesenchymal tumour of the urinary bladder
230014	Carcinoma transitional cell
280009	Tumour granular cell benign
280013	Haemangioma
32001.1	Tumour sex cord stromal mixed benign
320012	Tumour granulosa cell benign
320014	Cystadenoma
320015	Haemangioma
320017	Adenoma tubulostromal
320024	Tumour sertoli cell benign
340013	Polyp stromal
340014	Poiyp glandular
340016	Schwannoma benign
340021	Schwannoma malignant
340025	Tumour granular cell benign
340028	Sarcoma endometrial stromal
340030	Leiomyosarcoma
340031	Histiocytoma fibrous malignant
340032	Adenocarcinoma
410005	Adenoma pars distalis
410010	Adenoma pars intermedia
440113	Adenoma subcapsular cell mixed type
440114	Adenoma subcapsular cell type A
440115	Adenoma subcapsular cell type B
450001	Lymphoma malignant
450002	Tumour mast cell malignant
450003	Histiocytic sarcoma
460014	Haemangioma
460015	Haemangiosarcoma
470009	Haemangioma
500009	Thymoma benign
560005	Adenocarcinoma

560007	Adenoacanthoma malignant
570010	Haemangioma
570011	Schwannoma malignant
570013	Carcinoma basal cell
570017	Carcinoma sebaceous
570018	Carcinoma squamous cell
570021	Keratoacanthoma
570022	Histiocytoma fibrous malignant
570023	Haemangiosarcoma
580011	Sarcoma NOS
680009	Histiocytoma fibrous malignant
720004	Chondroma
760013	Lipoma
760018	Histiocytoma fibrous malignant
760028	Tumour granular cell benign
	-

APPEARS THIS WAY ON ORIGINAL

List of Organ/Tissue Type Codes Mouse

0101 0102 0103 0104 0211 0212 0213 0520	AORTA
0600 0800 0900	NOSE TRACHEA LUNGS
1501 1502	FORESTOMACH STOMACH, GLANDULAR
1601 1602 1603	JEJUNUM JEJUNUM
1702	ILEUM CECUM COLON
1703 1800	RECTUM LIVER
1900 2000	GALLBLADDER PANCREAS
2600 2600 2700	URINARY BLADDER EPIDIDYMIDES PROSTATE
	SEMINAL VESICLES OVARIES
3400 4100	UTERUS PITUITARY GLAND
4401 4500 4600	ADRENAL CORTEX HAEMOLYMPHORET. SYS. SPLEEN
4700 5000	BONE MARROW THYMUS
5104 5106	MESENT. LYMPH NODE
5600 5700 5800	MAMMARY GLAND SKIN/SUBCUTAN TISSUE SKELETAL MUSCLE
	EYES OPTIG NERVES
2500 7200	BODY CANTIES

7600 INJECTION SITE

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved OMB No. 0910-0338 Expiration Date April 30, 2000 See OMB Statement on last page

FOR FDA USE ONLY

APPLICATION NUMBER

	3	·	
APPLICANT INFORMATION			
NAME OF APPLICANT	•	DATE OF SUBMISSION	
Hoechst Marion Roussel, Inc.		10/21/99	
*ELEPHONE NO (Include Area Code) (816) 966-5000		FACSIMILE (FAX) Number ((816) 966-6794	
APPLICANT ADDRESS (Number, Stre Mail Code and U.S. License number if		State, ZIP Code, telephone	NAME & ADDRESS (Number, Street, 0 & FAX number) IF APPLICABLE
10236 Marion Park Drive Kansas City, Missouri 64134-06	27	Quintiles, Inc. (816) 767 P.O. Box 9708 Kensas City, MO 64134	-6674 or FAX: (816) 767-7373 -0708
PRODUCT DESCRIPTION			
NEW DRUG OR ANTIBIOTIC APPLICATION	NUMBER, OR BIOLOGICS LICENSE APP	LICATION NUMBER (If previous	ly issued) NDA 21-081
ESTABLISHED NAME (e.g., Proper name, U insuline glargine injection		PROPRIETARY NAME (trade nat	
CHEMICAL BIOCHEMICAL/BLOOD PRODU	CT NAME /H any)		CODE NAME (If any)
21 ^A -Gly-30 ^B a-L-Arg-30 ^B b-L-Arg			HOE 901
COSAGE FORM	STRENGTHS:	ROU	TE OF ADMINISTRATION:
Injection	100 U/mL	Sub	cutaneous
PROPOSED INDICATION(S) FOR USE.	daily subcutaneous administration in the treatment	of nations, with type 1 or type 2 diabetes	s meritus
whiteguise basa congrating) insulin for the cont		or parter to write type 2 or type 2	:
APPLICATION INFORMATION			
APPLICATION TYPE			
chéck é 🔀 NEW DRI	UG APPLICATION (21 CFR 314.50)	ABBREVIATED APPLICAT	ION (ANDA, AADA, 21 CFR 314 94
	BIOLOGICS LICENSE APPLICATION (21.0)	CFR part 601)	
FIAN NOA I DENTIFY THE APPROPE	RIATE TYPE S05 (b)	(1) 505 (b) (2)	507
FIAN ANDA OR AADA IDENTIFY TI Name : Drug	HE REFERENCE LISTED DRUG PRO	DUCT THAT IS THE BASIS F der of Approved Application	FOR THE SUBMISSION
THE OF SUBMISSION ORIGINA	AL APPLICATION AMENDM	ENT TO A PENDING APPLICATIO	RESUBMISSION
	NNUAL REPORT	BLISHMENT DESCRIPTION SUPP	LEMENT SUPAC SUPPLEME
EFFICACY SUPPLEMENT	LABELING SUPPLEMENT	HEMISTRY MANUFACTURING A	ND CONTROLS SUPPLEMENT OTHER
REASON FOR SUBMISSION			
In response to FDA re	equest, provide missing preclinical carcinogen	codes for Tumor	Type and Organ-Tissue
-		101th backsee bro	OVER-THE-COUNTER PRODUCT (O
PROPOSED MARKETING STATUS	(check one) PRESCRIPTION		
NUMBER OF VOLUMES SUBMITTED 1	N/A THIS APPLICATION	IS PAPER X P	APER AND ELECTRONIC LELECTRONI
ESTABLISHMENT INFORMATIO	N		
Provide ocations of all manufacturing, packs	iging and control sites for drug substance an	NECINING RIGHT SUCHOL (Abe or restr	s may be used if necessary). Include name, ing (e.g. Final dosage form, Stability testing)
conducted at the site. Please indicate wheth		TOWN IS SHE DO FROM .	
See original New Drug Application d	ated 4/09/99	E40/ble IDEs BMEs and D	MFs referenced in the current
Cross References (list related Licer	nse Applications, INDs, NDAs, PMAs	i, 310(K)5, IUCS, DMP5 200 U	mi = 1-9191911999 His 991.5
application)			
See Inchai New Orac Application d	Lated 4/09/99		

This a	applica	tion contains the following items: (Chec	k all that apply)		
	1.	Index			
	2.	Labeling (check one)	Draft Labeling	Final Printed	_abeling
	3.	Summary (21 CFR 314.50 (c))			
	4.	Chemistry section			
		A. Chemistry, manufacturing, and controls	information (e.g. 21 CFR	314.50 (d) (1), 21 CFR 601	.2)
		3. Samples (21 CFR 314.50 (e) (1), 21 CF	R 601.2 (a)) (Submit only	upon FDA's request)	
	(C. Methods validation package (e.g. 21 CF	R 314.50 (e) (2) (i), 21 Cl	FR 601.2)	
	5.	Nonclinical pharmacology and toxicology s	ection (e.g. 21 CFR 314.	50 (d) (2). 21 CFR 601.2)	
	6.	Human pharmacokinetics and bioavailabili	ty section (e.g. 21 CFR 3	314.50 (c) (3), 21 CFR 601.	2)
	7.	Clinical Microbiology (e.g. 21 CFR 314.50	(d) (4))		
	8.	Clinical data section (e.g. 21 CFR 314.50	(d) (5), 21 CFR 601.2)		
	9.	Safety update report (e.g. 21 CFR 314.50	(d) (5) (vi) (b), 21 CFR 60	01.2)	
	10.	Statistical section (e.g. 21 CFR 314.50 (d)	(6), 21 CFR 601.2)		
	11.	Case report tabulations (e.g. 21 CFR 314.	50 (f) (1), 21 CFR 601.2)		
		Case reports forms (e.g. 21 CFR 314.50 (1
	13.	Patent information on any patent which cla	ims the drug (21 U.S.C.	355 (b) or (c))	
	14	A patent certification with respect to any pa	atent which claims the dr	ug (21 U.S.C. 355 (b) (2) o	r (j) (2) (A))
	15	Establishment description (21 CFR Part 60	00, if applicable)		:
	16.	Debarment certification (FD&C Act 306 (k)(1))		
	17.	Field copy certification (21 CFR 314.5	(k) (3))		
	18	User Fee Cover Sheet (Form FDA 3397)			
	19.	OTHER (Specify)			
or abservable approved	rse reactions agreed to the ag	this application with new safety information about the pions in the draft labeling. I agree to submit safety update to comply with all applicable laws and regulations that od manufacturing practice regulations in 21 CFR 210 a logical establishment standards in 21 CFR Part 600, beling regulations 21 CFR 201, 606, 610, 660 and/or 80 he case of a prescription drug or biological product, pregulations on making changes in application in 21 CFR; guilations on reports in 21 CFR 314.80, 314.81, 600.80 call, state and Federal environmental impact laws, applies to a drug product that FDA has proposed for some Administration makes a final scheduling decision, immation in this submitissien have been reviewed and, to utily laise statement is a criminal offense, U.S. Code, titl.	e reports as provided for by regulapply to approved applications. Ind 211, 606, and/or 820. 9. scription drug advertising regulation 314.70, 314.71, 314.72, 314.97; and 600.81. cheduling under the Controlled South best of my knowlege are cer	ation or as requested by FDA. It till including, but not limited to the follow tions in 21 CFR 202 314.99, and 601.12.	s application is
L		RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE Lavonne Patton, Ph.D.		DATE 10/21/99
<u> </u>	aus		Director, Drug Regulato		10/21/99
FC 6	ox 9708.	ret. Citv. State. and ZIP Code) Mail Station: F3-M3028-		Telephone Number (816) 767-6000	
Public r	reporting	O 64134-0708) burden for this collection of information is estimate roes, gathering and maintaining the data needed, and correct or any other aspect of this collection of information, including the data respect of this collection of information, including the data respect of this collection of information, including the data respect to the da	completing and reviewing the coll	ection of information. Send comme	instructions, search ints regarding this
Paperwi Huber in 200 Indi Washing	en Resum Hump Hependen Igton: DC		person is not required	conduct or sponsor, and a to respond to a collection of isplays a currently valid OMB	
Please	DO NOT	RETURN this form to this address.			



Quintiles, Inc. Post Office Box 9708 Kansas City, MO 64134-0708 (816) 767-6000

CRIGINAL

ANG AMENDI

March 6, 2000

John Jenkins, MD **Acting Director** Division of Metabolic and Endocrine Drug Products Center for Drug Evaluation and Research (HFD 510) Food and Drug Administration Document Control Room 14B-04 5600 Fischers Lane Rockville, MD 20857

Subject:

NDA 21-081

insulin glargine injection

Amendment -Phase IV CMC Commitments

REVIEWS COMPLETED	
CSO ACTION	.o
	DATE

Dear Dr. Jenkins:

Quintiles Inc., as the US Agent for Aventis Pharmaceuticals Inc., has been authorized to communicate with the FDA on NDA 21-081.

The sponsor agrees to the following Phase IV CMC commitments in reply to a request received March 3, 2000 from Dr. Stephen Moore. (Please see the attached fax from the Agency.)

1.	when the 24-month sta	for the HOE 901 content, ability data on the primary stability lots of HOE 901 drug
	substance is available.	O. J. Co. 12 of the object of NIDA
	Protocol Submission:	Submitted in the original NDA
	Study Start:	Study on-going
	Final Report Submission:	No later than May 31, 2000
2.	The sponsor will re-evaluate the	
	related to the dru	g substance, when the 24-month stability data on the

primary stability lots of HOE 901 drug substance is available.

Submitted in the original NDA

Protocol Submission:

Susan M. Jordan

Study Start:

Study on-going

Final Report Submission:

No later than May 31, 2000

If you require any additional information, please contact me.

Sincerely,

Susan M. Zordan

Assistant Director, Regulatory & Technical Services

Quintiles, Inc. (Mail Stop: F3-M3026, Phone: (816) 767-6673)

REVIEWS COMPLETED CSO ACTION: DLETTER DN.A.I. DMEMO CSO INTIALS

FOOD AND DRUG ADMINISTRATION DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS 5600 FISHERS LANE, HFD-510 ROCKVILLE, MARYLAND 20857-1706 DATE: March 3, 2000



TO:

Name: Lavonne Patton, Ph.D.

Fax No: (816) 767-7373

Phone No.: (816) 767-6674

Location: Quintiles

Pages (including this cover sheet): 2

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone (301-827-6430) and return it to us at the above the above address by mail. Thank you

COMMENTS:

NDA 21-081 Lantus

Please provide your Phase 4 CMC commitments. Thank you.

CC: Onj NDA 21-081 HFD-510/DIV File HFD-510/Moore/Komandur

NDA 21-081 Lantus® (insulin glargine [rDNA origin])

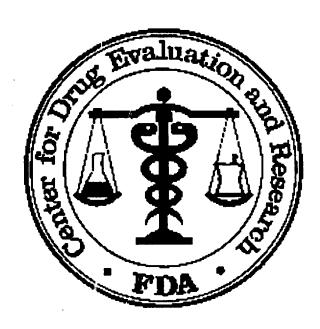
Date of submission: February 28, 2000

Chemistry, Manufacturing, and Controls Requests

Please provide your Phase 4 commitment for the following: 1. To re-evaluate the ______. for the HOE 901 content, _ when the 24-month stability data on the primary stability lots of HOE 901 drug substance is available. **Protocol Submission:** Submitted in the original NDA **Study Start:** Study on-going Final report submission: No later than May 31, 2000 2. To re-evaluate the related to the drug substance, when the 24-month stability data on the primary lots of HOE 901 drug substance is available. **Protocol Submission:** Submitted in the original NDA Study Start: Study on-going Final report submission: No later than May 31, 2000

Cleared for faxing by: /S/
Stephen Moore, Ph.D., Chemistry Team Leader I, DMEDP

FOOD AND DRUG ADMINISTRATION DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS 5600 FISHERS LANE, HFD-510 ROCKVILLE, MARYLAND 20857-1706 DATE: February 3, 2000



TO:

Name: Lavonne Patton, Ph.D.

Fax No: (816) 767-7373

Phone No.: (81

(816) 767-6674

Location: Quintiles (agent for Aventis)

Pages (including this cover sheet): 2

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone (301-827-6430) and return it to us at the above the above address by mail. Thank you

COMMENTS:

NDA 21-081 Lantus

Please provide your commitment for the Phase 4 study concerning the progression of retinopathy in patients with type 2 diabetes by February 10, 2000. Thank you.

CC: One NDA HF8-510/Dis File

Request for Phase 4 study commitment

Please provide your commitment to conduct a Phase 4 study to further evaluate the increased progression of retinopathy. The Phase 4 study should be a large simple trial in patients with type 2 diabetes with little or no background retinopathy. It should compare daily Lantus with twice daily NPH and should be powered to detect a two-fold increase in three step progression of retinopathy over one year with 90% power. The study should also include retinal photographs of all patients at baseline and at every 3-6 months in follow-up.

Please use the following timeline format for your commitment:

Protocol Submission:

X months after the approval

Study Start: Final Report Submission:

Y months after the approval Z months after the approval

Please submit your proposed commitment by February 10, 2000.

Cleared for faxing by:

APPEARS THIS WAY
ON ORIGINAL



Quintiles, Inc. Post Office Box 9708 Kansas City, MO 64134-0708 (816) 767-6000

ORIGINAL

September 2, 1999

Solomon Sobel, M.D.

Director, Division of Metabolic and Endocrine Drug Products

Center for Drug Evaluation and Research (HFD 516

Food and Drug Administration

Document Control Room 14B-04

5600 Fishers Lane

Rockville, MD 20857

Subject:

NDA 21-081

insulin glargine injection

HFD-5CMC Amendment

Dear Dr. Sobel:

Quintiles, Inc., as the US Agent for Hoechst Marion Roussel, has been authorized to communicate with the FDA on NDA 21-081.

This amendment contains the sterilization validation report for insulin glargine cartridges which was discussed at the pre-NDA teleconference with the FDA on December 17, 1998 and in telephone conversations with Dr. William Berlin on June 14-15, 1999. The sterilization validation report for cartridges was not available when the initial NDA was submitted

It was agreed with the Division that the information for cartridges could be filed as an amendment to the NDA no later than September 7, 1999.

The sterilization validation report for vials has been updated to include the installation of a

A revised version of this report for vials is also included in this amendment.

The vial and cartridge sterilization validation reports are in Volume 2 of this submission. An extra copy of this volume is included for the convenience of the chemistry and microbiology reviewers. Volume 1 of the submission contains several new or updated reports, which are described in more detail in the Introduction section of the submission.

If you have any questions, please contact me at (816) 767-6673.

Sincerely,

Susan M. Zordan

Assistant Director, Drug Regulatory Affairs

Quintiles, Inc.

P. O. Box 9708, Mail Station F3-M3026

Kansas City, MO 64134-0708

smh

REVIEWS COMPLETED

CSO ACTION:

LETTER N.A.I. MEMO

CSO INITIALS

DATE



Quintiles. Inc Post Office Box 9708 Kansas City. MO 64134-0708 (816) 767-6000

NEW CORRESP NSC

June 10, 1999₌

Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Attention:

Julie Rhee, Project Manager

Subject:

NDA 21-081

insulin glargine injection

Request for Marketing Exclusivity for insulin glargine

Dear Dr. Sobel.

Quintiles. Inc. as the US Agent for Hoechst Marion Roussel, has been authorized to communicate with the FDA on NDA 21-081.

Enclosed is a letter from Hoechst Marion Roussel. Inc. requesting extended marketing exclusivity for insulin glargine.

If you have any questions regarding the attached document, please do not hesitate to contact me at (816) 767-6674.

Sincerely.

Lavonne M. Patton, Ph.D.

Director, U.S. Drug Regulatory Affairs

Quint_es. Inc.

10245 Hickman Mills Drive

Kansas City, MO 64137

Enclosure

Letter from Hoechst Marion Roussel requesting Marketing Exclusivity

REC'D

JUN 1 1 1999

HFD-510

APPEARS THIS WAY

ON ORIGINAL

June 4, 1999

Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Hoechst Marion Roussel, Inc.

10230 Marion Park Drive Mail PO Box 9027 Kansas City MO 04134-0027 Telephone (816) 906-5000 US Web site www.hmrc.com

Subject:

NDA 21-081 insulin glargine

Request for Marketing Exclusivity

Dear Dr. Sobel,

This letter serves as an official request for a period of extended marketing exclusivity under 21CFR 314.50(j) and 21CFR 314.108(b)(2), for insulin glargine (New Drug Application April 9, 1999 and submitted to the Agency on April 22, 1999). As a new chemical entity, insulin glargine is entitled to five (5) years of exclusivity pursuant to 505(j)(4)(D)(ii) of the Federal Food. Drug and Cosmetic Act (21 U.S.C. 355). If you have any questions concerning this request, please contact:

Lavonne Patton, Ph.D. Quintiles, Inc. 10245 Hickman Mills Drive Kansas City, MO 64137 Phone: 816 767-6674

Sincerely.

J. Michael Nicholas, Ph.D. Director, Marketed Products

in A. C. HALL

U.S. Regulatory Affairs
Hoechst Marion Roussel, Inc.

Kansas City, MO 64137

APPEARS THIS WAY ON ORIGINAL

Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved OMB No. 0910-0338 Expiration Date April 30, 2000 See OMB Statement on last page

APPLICATION NUMBER

FOR FDA USE ONLY

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TELEPHONE NO Initialize Area Code) (816) 966-5000 APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail: Code and U.S. License number if previously issued): 10236 Marion Park Drive Kansas City, Missouri 64134-0627 ROBUCT DESCRIPTION New DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER of Previously issued): 10236 Marion Park Drive Kansas City, Missouri 64134-0627 ROBUCT DESCRIPTION New DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER of Previously issued): PRODUCT DESCRIPTION New DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER of Previously issued): PROPRIETARY NAME (rag. Proper name, USPICSAM name) Insuling lighting injection PROPRIETARY NAME (rag. Proper name, USPICSAM name) Insuling disting injection PROPRIETARY NAME (rag. Proper name, USPICSAM name) Insuling disting injection PROPRIETARY NAME (rag. Proper name, USPICSAM name) Insuling disting injection PROPRIETARY NAME (rag. Proper name, USPICSAM name) Insuling disting injection PROPRIETARY NAME (rag. Proper name, USPICSAM name) Insuling disting injection PROPRIETARY NAME (rag. Proper name, USPICSAM name) Insuling disting injection PROPRIETARY NAME (rag. Proper name, USPICSAM name) Insuling disting injection PROPRIETARY NAME (rag. Proper name, USPICSAM name) Insuling disting injection PROPRIETARY NAME (rag. Proper name, USPICSAM name) Insuling disting injection PROPRIETARY NAME (rag. Proper name, USPICSAM name) Insuling disting injection PROPRIETARY NAME (rag. Proper name, USPICSAM name) Insuling disting injection PROPRIETARY NAME (rag. Proper name, USPICSAM name) Insuling disting injection PROPRIETARY NAME (rag. Proper name, USPICSAM name) Insuling disting injection PROPRIETARY NAME (rag. Proper name) PROPRIETARY NAME (rag. Pr	NAME OF APPLICANT	· * * .			SION
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See original New Drug Application dated 4/09/99

1 Index 2. Labeling (check one) Draft Labeling Final Printed Labeling 3. Summary (21 CFR 314.50 (c)) 4. Chemistry section A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2) B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request) C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
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5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
9. Safety update report. (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
12 Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
14. A patent certification with respect to any patent which claims the drug. (21 U.S.C. 355 (b) (2) or (j) (2) (A))
15 Establishment description (21 CFR Part 600, if applicable)
16 Debarment certification (FD&C Act 306 (k)(1))
17 Field copy certification (21 CFR 314.5 (k) (3))
18 User Fee Cover Sheet (Form FDA 3397)
19 OTHER (Specify)
If agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings precaution or adverse reactions in the draft labeling. If agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved applications in comply with all applicable laws and regulations that apply of approved applications, including, but not limited to the following. 1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820. 2. Biological establishment standards in 21 CFR 2nt 600. 3. Labeling regulations 21 CFR 201, 606, 610, 660 and/or 809. 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202. 5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12. 6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81. 7. Local, state and Federal environmental impact laws. If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act. If agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision. The data and information in this submission have been reviewed and, to the best of my knowlege are certified to be true and accurate. Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT TYPED NAME AND TITLE Lavonne Patton, Ph.D.
Director, Drug Regulatory Affairs (Quintiles) 6/10/99
ADDRESS (Street. City. State, and ZIP Code) P O Box 9708. Mail Station: F2-M3026- Kansas City. MO 64134-0706 [816] 767-6000
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existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:
DHMS Reports Clearance Officer Paperwork Reduction Project (0910-0338) Project (0910-0

ORIGINAL



(816) 767-6000

June 4, 1999 T.

Solomon Sobel, M.D.

Director, Division of Metabolic and Endocrine Drug Products (HFD-510) Center for Drug Evaluation and Research

Document Control Room 14B-04

Quintiles, Inc. Post Office Box 9708 Kansas City MO 64134-0708

5600 Fishers Lane Rockville, MD 20857

Subject:

NDA 21-081

insulin glargine injection

Attention:

Julie Rhee

Dear Dr. Sobel,

Quintiles, Inc., as the US Agent for Hoechst Marion Roussel. has been authorized to communicate with the FDA on NDA 21-081.

Enclosed please find a copy of the diskette containing the proposed text of the labeling for HOE 901 in Word 6.0, originally submitted on April 27, 1999. I am enclosing a copy of the memo outlining the contents of this diskette for your information.

Please let me know if you require additional information.

Sincerely,

Lavonne M. Patton, Ph.D.

Monne Patter

Director, U.S. Drug Regulatory Affairs

Quintiles, Inc.

10245 Hickman Mills Drive

Kansas City, MO 64137

Phone: (816)-767-6674

REVIEWS COMPLETED CSU ACTION: LETTER N.A.I. MEMO **CSO INITIALS** DATE

Enclosure

Diskette containing the proposed text of the labeling for HOE 901 Original letter and memo from the April 27, 1999 submission





Quintiles Inc. Post Office Box 9708 Kansas City. MO 64134-0708 (816) 767-6000

Solomon Sobel, M.D.
Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD 510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject:

NDA 21-081 insulin glargine

Amendment to Pending Application:

SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY

DETERMINATION REQUESTED

Dear Dr. Sobel,

Quintiles, Inc., as the US Agent for Hoechst Marion Roussel, has been authorized to communicate with the FDA on NDA 21-081.

As discussed and agreed with the Agency (verbal contact of February 4, 1999), Hoechst Marion Roussel is submitting the report of the Pediatric Study (3003) conducted with insulin glargine for review with the original NDA dated April 9, 1999 and submitted on April 22, 1999.

This Pediatric Study is being supplied to the Agency in accordance with the Written Agreement from the Agency dated May 12, 1999 (copy attached). We understand that the submission of this study report makes the product eligible for FDAMA exclusivity of 6 months.

As noted in the cover letter of the original submission, the applicant has shown advantages in adults of insulin glargine compared to NPH in the frequency of the occurrence of clinically important severe and nocturnal hypoglycemic episodes. In the pediatric study 3003, equal maintenance of glycemic control (glycohemoglobin) and better fasting blood glucose control was also achieved in subjects treated with insulin glargine compared with NPH. As in the adult population, fewer subjects treated with insulin glargine reported nocturnal hypoglycemia, although the difference did not reach statistical significance in this smaller study. Therefore, the results observed in the pediatric population are consistent with the results of the adult population and represent a meaningful therapeutic benefit of insulin glargine.

The available treatment options to provide a basal insulin supply for children with diabetes are limited. The available treatments often provide inadequate glycemic control and are not currently labeled for pediatric use. We believe the results of our clinical studies and the need for additional treatment options for children with diabetes justifies consideration by the Agency to give insulin glargine priority review in accordance with the Center for Drug Evaluation and Research Priority Review Policy and the final Pediatric Rule.

The labeling currently submitted to the Agency regarding pediatrics will be reviewed based on the results of this study and proposed changes to the initially wording in the labeling will be submitted to the Agency for their consideration.

The pediatric study report is being submitted in triplicate, including an archival copy, medical review officer copy and statistical copy. A CD containing the PDF based electronic review aid is also being supplied with the report for the reviewer's convenience. The study report consists of 23 volumes with the pagination reflecting the volume number and page number. Item 16 (Debarment certification) and Item 19 (Financial Disclosure) on the 356h form are covered by the original NDA submission dated April 9, 1999 and submitted on April 22, 1999. The list of investigators associated with the financial disclosure statement can be found in Appendix A.2 (Volume 3) of the report.

Sincerely,

Lavonne M. Patton, Ph.D.

pronou m Patton

Quintiles, Inc.

10245 Hickman Mills Drive Kansas City, MO 64137 Phone: 816-767-6674

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES



Food and Drug Administration Rectivitie MD 20857

Hoechst Marion Roussel, Inc.
Attention: Lavonne Patton, Ph.D.
Director, Drug Regulatory Affairs at Quintiles, Inc.
U.S. Agent for Hoechst Marion Roussel, Inc.
P.O. Box 9708
Kansas City, MO 64134-0708

MAY 12 1999

Dear Dr. Patton:

Reference is made to your correspondence dated March 19, 1999, requesting a change to FDA's December 23, 1998, Written Request for pediatric studies for HOE 901 (insulin analog [rDNA origin] injection).

We have reviewed your proposed change and are amending the Written Request regarding the age groups accordingly. All other terms stated in our Written Request issued on December 23, 1998, remain the same.

Age groups in which study will be performed:
Ages 6 through 11 years
Ages 12 through 15 years

Reports of the studies that meet the terms of the Written Request dated December 23, 1998, as amended by this letter must be submitted to the Agency on or before June 30, 1999, in order to retain eligibility to qualify for pediatric exclusivity extension under Section 505A of the Act.

Reports of the studies should be submitted as an amendment to your pending application with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 2500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, contact Julie Rhee, Regulatory Project Manager, at (301) 827-6424.

Since by yours,

John K. Jeakins/M.D., F.C.C.P.

Director

Office of Drug Evaluation II

Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL





Quintries, Inc Post Office Box 9708 Kansas City, MO 64134-0708 816 767 6000 http://www.cro.quintries.com

Solomon Sobel, M.D.

Director, Division of Metabolic and Endocrine Drug Products

Center for Drug Evaluation and Research (HFD 510)

Food and Drug Administration

Center for Drug Evaluation and Research

Document Control Room 14B-04

5600 Fishers Lane

Rockville, MD 20857

Attention:

Central Document Room Park Building, Room 214 1240 Parklawn Drive Rockville, MD 20852

Subject:

New Drug Application insulin glargine injection

NDA 21-081

Dear Dr. Sobel.

In conformance with 21 CFR 314.1, Hoechst Marion Roussel, Inc. is submitting a New Drug Application for insulin glargine injection. The development of insulin glargine has been a collaborative effort between the applicant and the Reviewing Division at the FDA. This NDA provides support for the use of insulin glargine injection once-daily by subcutaneous administration for patients with diabetes mellitus who require a basal insulin for the control of hyperglycemia. The submission is 479 volumes in length.

In the analysis of the Phase III study results, the applicant has identified an advantage of insulin glargine compared to NPH human insulin in the frequency of the occurrence of clinically important hypoglycemic episodes. With equal maintenance of glycemic control (glycohemoglobin) and equal or better fasting glucose control in subjects treated with insulin glargine compared with NPH, significantly fewer subjects treated with insulin glargine reported severe and nocturnal hypoglycemia. A rationale for the observed advantage in clinical hypoglycemia is based on the smooth, peakless time-action profile of insulin glargine compared to that of NPH observed in Phase I studies. We believe these results justify consideration by the Agency to give insulin glargine priority review.

The applicant is cognizant in making this request for priority review of the discussions held with the Agency regarding the practical limitations of the reporting of admittedly subjective hypoglycemic symptoms by subjects in an open study design. However, in the process of data collection and analysis this limitation in the data has been taken into account and an attempt has been made to make the data as objective as possible. Several measures of hypoglycemia are reported, including all symptomatic hypoglycemic events with subsets of severe symptomatic hypoglycemia, using the DCCT definition of the patient requiring assistance of another person, and nocturnal symptomatic hypoglycemia. In addition, subjects were requested to determine blood glucose values at the time of the episode and episodes with blood glucose values less than 50 mg/dL and less than 36 mg/dL are presented. Furthermore, we have identified a subgroup of subjects reporting severe neurologic symptoms of hypoglycemia, including coma, convulsions and syncope. With progressively more restrictive and more clinically important definitions of hypoglycemia, the advantage of insulin glargine compared to NPH is more apparent. Finally, we have compared the frequency of hypoglycemic episodes to those reported in major clinical trials